



DRUG APPROVAL AND BIOEQUIVALENCE OVERVIEW

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ABSTRACT

Bioavailability is used to describe the fraction of an administered dose of medication that reaches the systemic circulation, one of the principal properties of the drug. By definition, when the drug is administered intravenously, its bioavailability is 100%. Bioequivalence studies compare both the rate and extent of absorption of various multisource drug formulations with the innovator (reference) product, on the basis that if two formulations exhibit similar drug concentration time profile in the blood/plasma, they should exhibit similar therapeutic effects. Numerous papers in the literature indicate that there is concern that the current standards for approval of generic drugs may not always ensure therapeutic equivalence. The availability of different formulations of the same drug substance given at the same strength and in the same dosage form poses a special challenge to health care professionals. Once bio-equivalence has been established via bioavailability testing in a statistically significant manner subsequent batches of the same product are deemed bio-equivalent based on in-vitro measures such as drug dissolution.

KEYWORDS: *Bioavailability, Bioequivalence studies, Replication.*

INTRODUCTION

Bioavailability is used to describe the fraction of an administered dose of medication that reaches the systemic circulation, one of the principal properties of the drug. By definition, when the drug is administered intravenously, its bioavailability is 100%. However when a medication is administered via other routes (such as by mouth), its bioavailability decreases (due to incomplete absorption and first-pass metabolism). Bioavailability is one of the essential tools in pharmacokinetics, as bioavailability must be considered when calculating dosage for non-intravenous route of administration.

Bioavailability and Bio equivalence of drug products and drug product selection have emerged as critical issues in pharmacy and medicine during the last three decades. Concern about lowering health care costs is resulted in a tremendous increase in the use of generic drug products currently about one half of all prescriptions written are for drugs that can be substituted with a generic product.

This phenomenal growth of the generic pharmaceutical industry and the abundance of multi-source products have prompted some questions among many health professionals and scientists regarding the therapeutic equivalency of these products. Inherent in the currently accepted guidelines for product substitution is the assumption that a generic drug considered to be Bioequivalent to a brand-name drug would elicit the same clinical effect.

Numerous papers in the literature indicate that there is concern that the current standards for approval of generic drugs may not always ensure therapeutic equivalence. The

availability of different formulations of the same drug substance given at the same strength and in the same dosage form poses a special challenge to health care professionals.

If the size of the dose to be administered is same, then bioavailability of a drug from its dosage form depends upon three major factors:

1. Pharmaceutical factors related to physicochemical properties of the drug and characteristics of dosage form.
2. Patient related factors.
3. Route of administration.

If the goal is to compare the two formulation of same drug then the experimental design should maintain the remaining factors constant. The resultant bioavailability may differ with respect to the amount absorbed, the rate of absorption or both. The bioavailability fraction is the fraction of the administered dose that enters systemic circulation.

$$f = \text{Bioavailable Dose} / \text{Administered Dose}$$

Bioavailability reflects the extent of the systemic availability of the 'area under the concentration time curve' (AUC), the peak plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}). The extent of the systemic availability is determined by the extent of drug absorbed from the site of administration. For a drug that obeys linear pharmacokinetics, the AUC and C_{max} values increase proportionately with the dose. Consequently, if two formulations / dosage form of the same drug exhibit comparative AUC values, they are considered to have similar systemic availability. The bioavailability of an oral dosage form or a drug is generally compared with an intravenous solution (100% standard), to determine the absolute bioavailability.

Comparative Bioavailability: a universal approach

Most bioavailability studies, whether for a new or generic product, possess a common theme. A test conducted to identify the quantitative nature of a specific product comparison. This comparison for a new may be, for example, to assess the performance of an oral formulation relative to that of an intravenous dose or perhaps the performance of a modified-release formulation in comparison to a conventional capsule. For a generic product, it is typically a comparison of a competitive formulation with a reference product. Such commonality surrounding comparative bioavailability studies suggests a universal experimental approach.

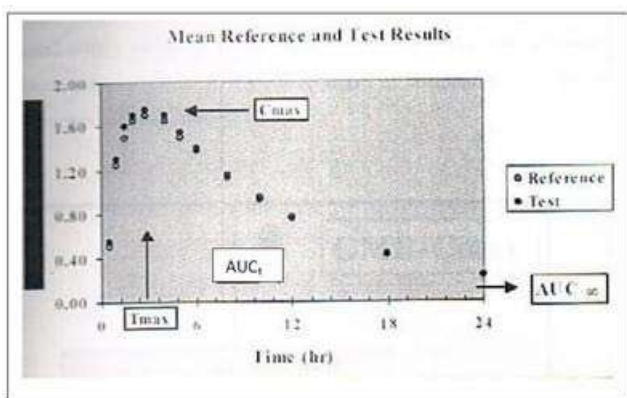


Figure 1: illustration of the key metrics in a comparative bioavailability trial showing, for example, Test and Reference products. The maximum concentration (C_{max}) occurs at the T_{max} .

From the figure 1, the two primary metrics for such concentration versus time profiles are the area under the curve (AUC) and the maximum observed concentration (C_{max}); the former customarily includes the AUC to the last sampling time in a trial (AUC_t) and the extrapolated total AUC to time infinity (AUC_{∞}). The time at the maximum concentration (T_{max}) is also of some minor interest.

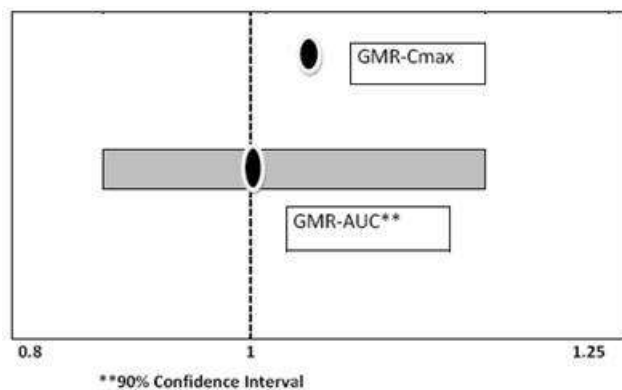


Figure 2: an illustration of the statistical criteria to be satisfied to gain equivalence status in a comparative bioavailability assessment. For example, in a

bioequivalence trial, the geometric mean ratio for the test/reference C_{max} (GMR C_{max}) must be located between 0.8 and 1.25. The GMR AUC's (whether AUC_t or AUC_{∞}) and their computed 90% confidence intervals reside completely within the 0.8 to 1.25.¹⁻¹⁰

The AUC_t is the total area under the concentration versus time profile to the last sampling time. The area to computing the metrics, conclusions need to be reached regarding the comparison. Statistical methods are applied to test if the metrics are sufficiently similar to be considered equivalent. When the metrics are deemed equivalent, the drug concentration profiles are regarded as fundamentally the same. To achieve this equivalence, the study products geometric mean ratios (eg. $AUC_{test} / AUC_{reference}$), as well as their projected 90% confidence intervals for the population mean ratio, must be located within an 80 to 125% window. For the maximum concentration (C_{max}) some regulatory agencies consider it adequate if only the mean ratios are within the interval.

Measurement of Bioavailability¹¹

The methods useful in quantitative evaluation of bioavailability can be broadly divided into two categories:

- Pharmacokinetic method
- Pharmacodynamic Method

A) Pharmacokinetic Method¹¹

These are very widely used and based on the assumption that the pharmacokinetic profile reflects the therapeutic effectiveness of a drug. Thus, these are indirect methods.

The two major pharmacokinetic methods are:

- Plasma level-time studies.
- Urinary excretion studies.

B) Pharmacodynamic Method¹¹

These methods are complementary to pharmacokinetic approaches and involve direct measurement of drug effect on a (patho) physiological process as a function of time. The two pharmacodynamic methods involve determination of bioavailability from:

- Acute Pharmacological Response.
- Therapeutic Response.

BIOEQUIVALENCE

Bioequivalence gained increasing attention during the last 40 years after it became evident that marketed products having the same amounts of the drug may exhibit marked differences in their therapeutic responses. Generally, these differences were well correlated to dissimilar drug plasma levels caused mainly by impaired absorption. Now a considerable body of evidence has accumulated indicating that drug response is better correlated with the plasma concentration or with the amount of drug in the body than with the dose administered. Consequently, on the basis of simple pharmacokinetic concepts and parameters, bioavailability and bioequivalence studies have been established as acceptable surrogates for expensive, complicated and lengthy clinical trials and



are used extensively worldwide to establish and ensure consistent quality and a reliable, therapeutically effective performance of marketed dosage forms.

The present day bio equivalence studies are too complicated, expensive and difficult to be carried out. Two of the reasons for this difficulty are the need for many healthy volunteers and withdrawing 10-20 blood samples from an indwelling catheter from each volunteer spanning over a long period of time. Same procedure has to be repeated after a washout period, substituting the reference and test samples in the volunteers. The entire have to be chemically analyzed and the collected data subjected to elaborate statistical analysis. The parameter 'area under the curve' can have nearly the same values for vastly.

Bioequivalence products as it reflect only the total amount of drug reaching the systemic circulation. Bioequivalence studies compare both the rate and extent of absorption of various multisource drug formulations with the innovator (reference) product, on the basis that if two formulations exhibit similar drug concentration- time profile in the blood/plasma, they should exhibit similar therapeutic effects three situations have thus been defined in which bioequivalence studies are required

- When the proposed marketed dosage form is different from that used in pivotal clinical trials.
- When significant changes are made in the manufacture of the marketed formulation.
- When a new generic formulation is tested against the innovator's marketed product.

Comparative evidence may require not only studies in a fasting condition, but following a specified meal. The later permit drug formulations to be evaluated under 'stressed conditions'. If it is shown that competitive products are bioequivalent under both fasting and fed conditions, there is greater confidence that they are therapeutically equivalent when used in patients. Bio-equivalent simply means that one brand or dosage form of a drug or supplement is equivalent to a reference brand or dosage form of the same drug or supplement in terms of various bioavailability parameters measured via in-vivo testing in human subject. Bio-equivalence cannot be claimed based on in-vitro testing only or on the basis of animal studies only. Bio-equivalence of human drugs must be determined in humans via established measures of bioavailability. By the same taken animal drugs must be tested for bio-equivalence in the animal species for which the drug in intended. Once bio-equivalence has been established via bioavailability testing in a statistically significant manner subsequent batches of the same product are deemed bio- equivalent based on *in-vitro* measures such as drug dissolution.

There is no such thing as increased bioequivalence. The statement of increased bioequivalence makes no sense. A product can be either bio-equivalent or bio-in equivalent. A product can't be more bio-equivalent or less bio- equivalents.¹²

Comparative bioavailability for generic drug products (ANDA) - Bioequivalence Studies

The deductive inference concept is also central to bioequivalence testing. The foundation is set, first, through evidence that a specified, approved, reference drug product (e.g. tablet from the innovative manufacturer) has shown acceptable safety and efficacy through an array of clinical trials.

Second, a widely held view is embraced that the time-dependent drug concentrations in blood from such a reference product are intimately linked with the therapeutic effects.

Third, a principle is adopted, namely that chemically equivalent (same amount of the same active ingredient) and pharmaceutically equivalent products (same dosage form; e.g. conventional tablet), that exhibit the same rate and extent of drug absorption, are bioequivalent. Fourth, bioequivalent products by inference are considered therapeutically equivalent.

When a manufacturer thereby wishes to gain therapeutic equivalence by introducing a competitive generic product into the marketplace, it is not necessary to conduct the full array of trials needed for the first (innovative) product. If equivalence has been demonstrated, according to prescribed study requirements, appropriately determined metrics (Figure 1), and statistical criteria (Figure 2), the generic product by inference is regarded as therapeutically equivalent to the innovative drug product.

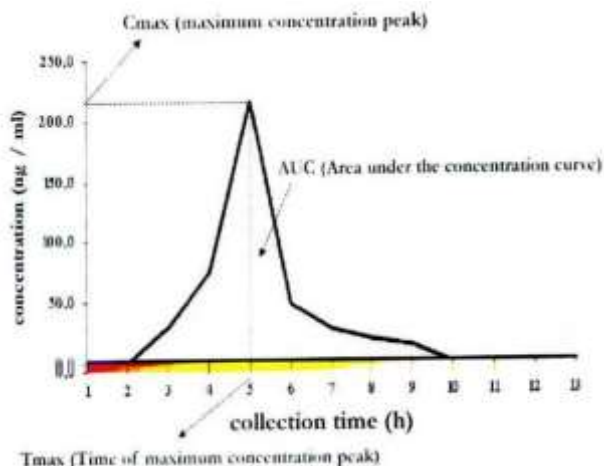
The design of and requirements in, bioequivalence studies are fundamentally satisfied through single dose administrations, although there is a lingering interest in multiple dose testing. The focus is on the rate and extent of absorption of the active ingredient, although some jurisdictions (e.g. FDA) continue to show an interest in the primary active metabolite(s).

In some cases, notably drugs that exhibit non-linear pharmacokinetics, the dose strength to be tested may be dictated by whether the drug's non-linearity is attributable to the absorption or elimination phase (Health Canada). As a general principle, the studies are designed to test inherent product absorption properties. Thereby, the trials generally specify healthy normal controls that exhibit circumscribed demographics.

Pharmacokinetic Measurement^{11, 17, 18}

Direct (e.g., rate constant rate profile) and indirect (e.g., C_{max}, T_{max}, mean absorption time, mean residue time, C_{max} normalized to AUC) pharmacokinetic measurements are limited in their ability assess rate of absorption.

From these direct or indirect measurements of absorption rate to measures of systemic exposure. C_{max} and AUC can continue to be used as measures for product quality BA and BE, but more in terms of their capacity to reflect rate and extent of absorptions.

**Figure 3****Before Peak Concentration**

For orally administered immediate release drug products, BE may generally be demonstrated by measurement of peak and total concentration. An early concentration measure may be indicated on the basis of appropriate clinical efficacy/safety trials and/or pharmacokinetic / pharmacodynamic studies that call for better of drug absorption into the systemic circulation (e.g., to ensure rapid onset of an analgesic effect or to avoid an excessive hypotensive action of an antihypertensive). In this recommends use of partial AUC as a Before Peak Concentration. The partial area should be truncated at the population median of Tmax values for the reference formulation. At least two quantifiable samples should be collected before the expected peak time to allow adequate estimation of the partial area.

Peak Concentration

Peak concentration should be assessed by measuring the peak drug concentration (Cmax) obtained directly from the data without interpolation.

Total Concentration

For single dose studies, the measurement of total concentration should be: Area under the plasma/serum/blood concentration-time curve from time zero to time t (AUC_{0-t}), where t is the last time point with measurable concentration for individual formulation, Area under the plasma/serum/blood concentration-time curve from time zero to time infinity. (AUC_{0-∞}), where AUC_{0-∞} = AUC_{0-t} + Ct/z, Ct is the last measurable drug concentration and z is the terminal or elimination rate constant calculated according to an appropriate method. The terminal half-life (t_{1/2}) of the drug should also be reported.

The following pharmacokinetic parameters are required for submission:

- Plasma concentrations and time points.
- Subject, period, sequence, treatment.
- AUC_{0-t}, AUC_{0-∞}, Cmax, Tmax, and t_{1/2}.
- Inter subject, intra subject, and/or total variability, if

available.

- Cmin (concentration at the end of a dosing interval).
- Cav (average concentration during a dosing interval).
- Degree of fluctuation [(Cmin-Cmin)/av].
- Swing [(Cmax-Cmin)/Cmin] if steady state studies are employed.

The following statistical information required for AUC_{0-t}, AUC_{0-∞}, and C max:

- Geometric mean
- Arithmetic mean
- Ratio of mean
- Confidence intervals

Logarithmic transformation should be provided for measures used for BE demonstration.

Rounding off of confidence interval values

Confidence interval (CI) values should not be rounded off; therefore, to pass a CI limit of 80-125, the values should be at least 80.00 and not more than 125.00.^{12, 13, 18}

GENERAL CONCEPT OF DESIGN AND CONDUCT OF STUDIES

The design and conduct of the study should follow EC- rules for good clinical practice, including reference to an Ethics Committee.

As recommended by the US FDA (1992), in most bioequivalence trials, a 'test' formation is compared with the standard / innovator 'reference' formulation, in a group of normal, healthy subjects (18-55 yr), each of whom receive both the treatments alternately, in a crossover fashion (two-period, two-treatment crossover design), with the two phases of treatment separated by a 'washout period' of generally a week's duration, but may be longer (a minimum time equivalent to 5 half-lives) if the elimination half-life of the drug is very long. The treatment is assigned to each subject, randomly, but an equal number of subjects receive each treatment in each phase. Thus, in case of two treatments A and B, one group gets the treatment in the order AB and the second group in the reverse order BA. This is done to avoid the occurrence of possible sequence or period effects. A similar allocation is done in case of a three treatment crossover design (three-period, three-treatment crossover design).

For several drugs great-subject variability in clearance is observed. The intra-subject coefficient of variation (approximately 15%) is usually substantially smaller than that between subjects (approximately 30%), and therefore, crossover designs are generally recommended for bioequivalence studies.

The primary advantage of the crossover design is that since the treatments are compared on the same subject, the inter subject variability doesn't contribute to the error variability. If the drug under investigation and/or its metabolites has an extremely longer half-life, a parallel group design may be indicated. In a parallel group design,



subjects are divided randomly into groups, each group receiving one treatment only. Thus, each subject receives one treatment only. In a parallel design, although one doesn't have to worry about sequence, period or carry over effects, or dropouts during the study, the inter – subject variability being very high, the sensitivity of the test is considerably reduced, thus requiring a larger number of subjects compared to a crossover design, to attain the same sensitivity.

Inherent in both the crossover and parallel designs are the three fundamental statistical concepts of study design, namely

- Randomization
- Replication and Error control

Randomization

It implies allocation of treatments to the subjects without selection bias. Consequently, Randomization is essential to determine an unbiased estimate of the treatment effects.

Replication

It implies that a treatment is applied to more than one experimental unit (subject) to obtain more reliable estimate than is possible from a single observation and hence provides a more precise measurement of treatment effects. The number of replicates (sample size) required will depend upon the degree of difference to be detected and inherent variability of the data. Replication is used concomitantly with “Error Control” to reduce the experimental error or error variability.¹⁴

More commonly used replicated crossover designs to compare two formulations are:

- Four sequence and two-period design (Balaam's Design)
- Two sequence and four-period design
- Four sequence and four-period design
- Two sequence and three-period design
- Crossover design for three medications (William's Design)
- Crossover design for four medications (William's Design)

Crossover design for two medications (T-test; R=reference)

➤ 2x2 crossover design

This is a conventional not-replicated design with formulations, two periods, two sequences that may be represented as follows:

Table 1: 2x2 Crossover Design

Sequence	Period	
	1	2
1	R	T
2	T	R

Each individual is randomly assigned to RT or TR sequence in two dosage periods. That is, individual assigned to RT (TR) sequence receive formulation R (T) in the first dosage period and formulation T (R) in the second dosage period. Randomization for a 2x2 crossover study may be carried out through tables of random numbers or randomization procedures implemented by statistical software.

➤ Replicated crossover design

This design is recommended for bioequivalence studies of formulations with modified-release dosage or highly variable products (intra-individual variation coefficient $\geq 30\%$), including the quick release ones and other oral administration products.

The same test and reference formulation batches shall be used for this design for replicated administration. The periods shall be sufficiently spaced (washout) to assure non-existence of carryover effects.²³

More commonly used replicated crossover designs to compare two formulations are:

Table 2: Two sequence and four-period design

Sequence	Period			
	1	2	3	4
1	T	R	R	T
2	R	T	T	R

Table 3: Four sequence and four-period design

Sequence	Period			
	1	2	3	4
1	T	T	R	R
2	R	R	T	T
3	T	R	R	T
4	R	T	T	R

Table 4: Two sequence and three-period design

Sequence	Period		
	1	2	3
1	T	R	T
2	R	T	R

**Table 5: Crossover design for three medications (william's design)¹⁵**

Sequence	Period		
	1	2	3
1	R	T2	T1
2	T1	R	T2
3	T2	T1	R
4	T1	T2	R
5	T2	R	T1
6	R	T1	T2

(William's design with T1 = test, T2 = test, R = Reference)
In order to compare three formulations of a drug, there are a total of three possible comparison pairs among formulations: formulation-1 versus formulation-2, formulation-1 versus formulation-3, and formulation -2 versus formulation =3.¹⁵

Table 6: Crossover Design For Four Medications (William's Design)¹⁵

Sequence	Period			
	1	2	3	4
1	R	T3	T1	T2
2	T1	R	T2	T3
3	T2	T1	T3	R
4	T3	T2	R	T1

PROTOCOL DESIGNING

General Information

- Product title, number and date.
- Confidentiality paragraph.
- Name and address of the sponsor and monitor (in the event he is not the sponsor).
- Name and address of the clinical laboratories.
- Names and titles of the investigators and co-investigators.

Information on the Study Design

- Study type and design.
- Primary and secondary objectives.
- Description of the randomization and blinding procedure. Study treatments and dosages regimen, including package and label information.

Information on study population

- Number of patients.
- Duration of subject participation.
- Informed consent form.
- Maintenance of the randomization codes and procedures for code break (double-blind study)

Selection and Discontinuation

- Inclusion criteria.
- Exclusion criteria.
- Compliance monitoring method.
- Patient discontinuation criteria: when and how to discontinue; type of to be collected; subject replacement; discontinued follow up.
- Subject treatment; Names of all products, doses, dose escalation, administration routes, treatment period and follow up period; allowed and forbidden treatment/medication, before and during the study.

Efficacy and Safety evaluation

- Specification of the efficacy and safety parameters.
- Methods and time points to evaluate record and analyze these parameters.
- Type and duration of subject follow-up after the occurrence of an adverse event.
- Procedures for the recording and reporting of adverse events and intercurrent illnesses.

Conduction of the study

- Monitoring frequencies.
- Audits.
- Data and records maintenance.
- Publication policy.
- Procedures to monitor subject compliance.

Others

- Clinical laboratory parameters.
- Concomitant therapy.
- Documentation of investigator's approval and date (signature page)
- Funding and insurance.
- Direct access.
- Ethics.^{19, 20}

APPLICATION FOR PRODUCT CONTAINING NEW ACTIVE SUBSTANCES

Bioavailability

In the case of new active substances (new chemical entities) intended for systemic action the pharmacokinetic characterization will have to include the determination of the systemic availability of the substance in its intended pharmaceutical form in the comparison with intravenous administration. If this is not possible the bioavailability relative to a suitable oral solution or standardized suspension should be determined. In the case of a prodrug the intravenous reference solution should preferably be the therapeutic moiety.

Bioequivalence

The dosage recommendations for the market form of a new active substance should be validated by a comparative bioavailability study against the forms used in the clinical trials, especially those used in the dose finding studies, unless its absence can be justified by satisfactory in vitro data.¹⁶



APPLICATIONS FOR PRODUCTS CONTAINING APPROVED ACTIVE SUBSTANCES

Bioequivalence Studies

Bioequivalence is required if a product is intended to be substituted for an approved medicinal product. Requirements for the demonstration of Bioequivalence may vary with this type of product.

Oral Immediate Release Products with Systemic Action

Bioequivalence studies should be performed for all immediate release products intended for systemic action unless, considering all of the following criteria, the applicant can establish that in vitro are sufficient to ensure Bioequivalence.

As an example in vitro data alone would be acceptable if all of the following criteria are fulfilled, as follows:

- A) The active substance is known not to require special precautions with respect to precision and accuracy of dosing, e.g., it does not have a narrow therapeutic range.
- B) The pharmacokinetics is characterized by a pre-systemic elimination / first pass metabolism less than 70% and linear pharmacokinetics within the therapeutic range.
- C) The drug is highly water soluble i.e., the amount contained in the highest strength is dissolved in 250ml of each of three pharmacopoeial buffers within the range of pH 1-8 at 37°C (preferably at or about pH 1.0,4.6,6.8).
The drug is permeable in the intestine, i.e., its extent of absorption is greater than 80%. Permeability of a drug substance can be determined by different methods, such as in vivo (e.g., CaCO₂ cell cultures) and in situ (e.g., intestinal perfusion in animals). The choice of the method has to be justified by the applicant in terms of ability to predict the rate and extent of absorption in humans. Stability of the drug should be documented under various conditions typical for the gastrointestinal tract.
- D) The excipients included in the composition of the medicinal product are well established and no interaction with the pharmacokinetics of the active substance is expected.^{21, 22}

Oral Solutions

If the product is an aqueous oral solution at time of administration containing the active substance in the same concentration and form as a currently approved medicinal product, not containing excipients that may affect gastrointestinal transit or absorption of the active substance, then a bioequivalence study is not required.

In those cases where an oral solution has to be tested against a solid dosage form (e.g., an oral solution is formulated to be equivalent to an existing tablet), a comparative bioavailability study will be required unless an exemption can be justified (see 5.1.1).^{21, 22}

Modified Release Dosage Form

Modified Release products include delayed-release products such as enteric-coated dosage forms and extended (controlled)-release products. Bioequivalence studies for delayed-release drug products are similar to those for extended-release drug products. Extended-release products can be capsules, tablets, granules, pellets and suspensions. For extended-release and delayed-release drug products, the following studies are recommended.

- A single dose, non replicate, fasting study comparing the highest strength of the test and reference listed drug product.
- A food-effect, no replicate study comparing the highest strength of the test and reference product.

Fixed Combination Product

Combination of product should be assessed with respect to the bioavailability and bioequivalence of individual active substance either separately or as an existing combination.

Parenteral Formulations

The applicant is not required to submit a bioequivalence study if the product is to be administered as an intravenous solution containing the active ingredient in the same concentration as the currently authorized product.

In the case of other routes, e.g., intramuscular or subcutaneous, the product must be the same type of solution (aqueous or oily), contain the same concentration of the active substance and the same or comparable excipients as the medicinal product currently approved for this exemption to apply.

Gases

If the product is a gas for inhalation a bioequivalence study is not required.

Locally Applied Products

For products for local use (after oral, nasal, ocular, dermal, rectal, vaginal, etc) administration intended to act without systemic absorption the approach to determine bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are in principle required (see specific Note for Guidance).

In Vitro Dissolution

Dissolution studies are required either as complementary (see 3.10) or surrogate to bioequivalence studies and must follow the guidance as laid out in Appendix - 4. In the later case similarity of dissolution profile between test product and reference product based on discriminatory tests should be demonstrated.²¹

Variations

If a product has been reformulated from the

formulation originally approved or the manufacturing method has been modified by the manufacturer in ways that could be considered to impact on the bioavailability, a bioequivalence study is required, unless otherwise justified. Any justification presented should be based upon general considerations, e.g., as per 5.1.1, or on whether an acceptable *in vivo*/ *in vitro* correlation has been established.

In cases where the bioavailability of the original product has been investigated and an acceptable correlation between *in vivo* performance and *in vitro* dissolution rate has been established, the requirements for the bioequivalence can be waived if the dissolution rate *in vitro* of the new product is similar with that of the already approved medicinal product under the same test conditions as used to establish the correlation. In all other cases bioequivalence studies have to be performed.

When variations to an essentially similar product are made in the reference product for the bioequivalence study should be the innovator's product.²³

Dose Proportionality in Oral Form

If a new application concerns several strengths of the active substance only one bioequivalence study with the highest strength is necessary (unless a lower strength is chosen for reasons of safety) provided that the pharmaceutical products are manufactured by the same manufacturer, at the same manufacturing site and all of the following conditions hold:

- Pharmacokinetics has shown to be linear over the therapeutic dose range.
- The qualitative composition of the different strengths is the same.
- The ratio between active substance and the excipients is the same or in the case of preparations containing a low concentration of the active substance, the ratio between the excipients is the same.
- The dissolution profile should be similar under identical conditions for the additional strength of the batch used in the bioequivalence study.

If a new strength is applied for on the basis of an already approved medicinal product and all of the stated conditions hold then a bioequivalence study is not necessary.²⁴

Suprabioavailability

If a suprabioavailability is found, i.e. if the new product displays a bioavailability appreciably larger than the approved product, reformulation to lower dosage strength should be performed. The biopharmaceutical development should be reported and a final comparative bioavailability study of the reformulated new product with the old approved product should be submitted.

In case of reformulation is not carried out the dosage recommendation for suprabioavailable product will have to be supported by clinical studies is different from the reference product. Such a pharmaceutical

product should not be accepted as therapeutic equivalent to the existing reference product should not accepted as therapeutic equivalent to the existing reference product and if marketing authorization is obtained the new product may be considered as a new reference product.^{22, 25}

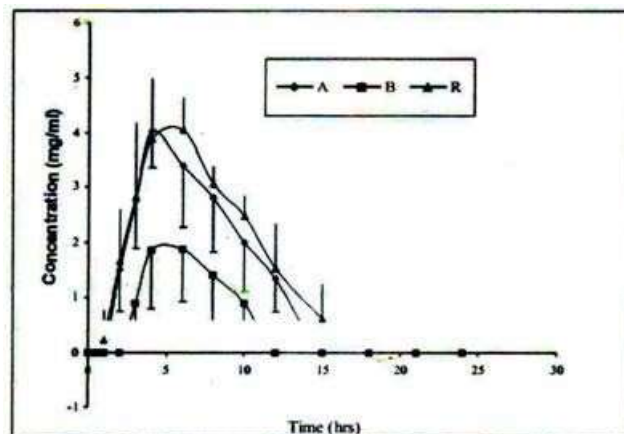


Figure 4: Mean plasma concentration (\pm SD) vs Time profile

ACCEPTANCE CRITERIA FOR BIOEQUIVALENCE STUDIES

The pharmacokinetic characteristics to be tested, the procedure for testing and the acceptance ranges should be stated before hand in the protocol. In studies to determine average Bioequivalence the accepted ranges for the main characteristics are:

AUC-ratio

The 90% confidence interval for this measure of relative bioavailability should lie within an acceptance range of 0.80-1.25. In case of an especially narrow therapeutic range the acceptance range may need to be tightened. In rare cases (e.g. highly variable drugs) a wider acceptance range may be acceptable if it is based on sound clinical justification.

Cmax-ratio

This measure of relative bioavailability may be more variable than the AUC-ratio and a wider acceptance range may be acceptable. The range used should be justified in the protocol taking into account safety and efficacy consideration.

Tmax-diff

Statistical evaluation of Tmax only makes sense if there is a clinically relevant claim for release or action or signs for a relation to adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically determined range.

Others: For others pharmacokinetic parameters (e.g. Cmin, Fluctuation, $t_{1/2}$, e.t.c..) considerations to those for



AUC, C_{max}, t_{max} apply. [25]

History of Generic Drug Approval

As recently as 40 years ago, drug companies could release new products with far less testing than is required today the real test of a drug's safety and effectiveness came after it went to market. If too many patients had bad reactions, the drug could be pulled off the shelves. The danger of this approach became tragically clear when the sedative thalidomide caused thousands of devastating birth defects in Europe, Canada, Latin America, Africa, and Asia (6).

In 1970 FDA established the ANDA as a mechanism for the review and approval of generic versions.

Before 1978, generic product applicants were required to submit complete safety and efficacy through clinical trials Post 1978,

Applicants were required to submit published reports of such trials documenting safety and efficacy.

Neither of these approaches was considered satisfactory and so originated Hatch Waxman Act on 1984 (7).

Indispensability grounds for Generics (8)

Contain the same active ingredients as the innovator drug (inactive ingredients may vary).

Must be identical in strength, dosage form, and route of administration.

Must have same use/indications

Must be bioequivalent.

Must have same batch requirements for Identity, Safety & Purity.

C) Must follow strict standards of FDAs GMPs.

D)

Related act's to the ANDA Submission

Hatch-Waxman Act

The Drug Price Competition and Patent Term Restoration Act (known as the "Hatch-Waxman Act" enacted in 1984. In 1984, Congress enacted the Hatch-Waxman Act as an amendment to the Federal Food, Drug, and Cosmetic Act (the "FFDCA") and the Patent Act. The two main goals are to encourage innovation in pharmaceutical research and development and to help generic drugs reach the market more quickly (9). "The Hatch-Waxman Act is an act dealing with the approval of generic drugs and associated conditions for getting their approval from FDA, market exclusivity, rights of exclusivity, patent term extension and Orange Book Listing."

General provisions of the act

Creation of section 505(j), Section 505(j) established the ANDA approval process. The timing of an ANDA approval depends in part on patent protections for the innovator drug NDA must include any patent that claims

the "drug" or a "method of using [the] drug" for which a claim of patent infringement could reasonably be asserted. On approval of NDA, FDA publishes patent information for drug in Orange Book ("Approved Drug Products with Therapeutic Equivalence Evaluations") (10).

Objective of the act

FDA publishes patent information on approved drug products in the Orange Book

Maintaining list of patents which would be infringed.

Only Bioavailability studies and not clinical trials needed for approval.

Para I, II, III and IV certifications

Data exclusivity period for New Molecular Entities.

Extension of the original patent term.

The "Bolar" Provision (10)

Recent additions to the Hatch-Waxman Act Under the "Medicare Prescription Drug and Modernization Act", 2003

Non-extension of the 30-month period

Time limit for informing patent owner.

Provision for allowing declaratory judgment.

Benefit of exclusivity for several ANDAs filed on same day allowed (10)

ANDA certification clauses

ANDA has four types of the Submissions. ANDA applicants must certify to each patent for the Reference Listed Drug

Paragraph I – patent not submitted

Paragraph II – patent has expired

Paragraph III – date patent will expire

Paragraph IV – patent is invalid or will not be infringed

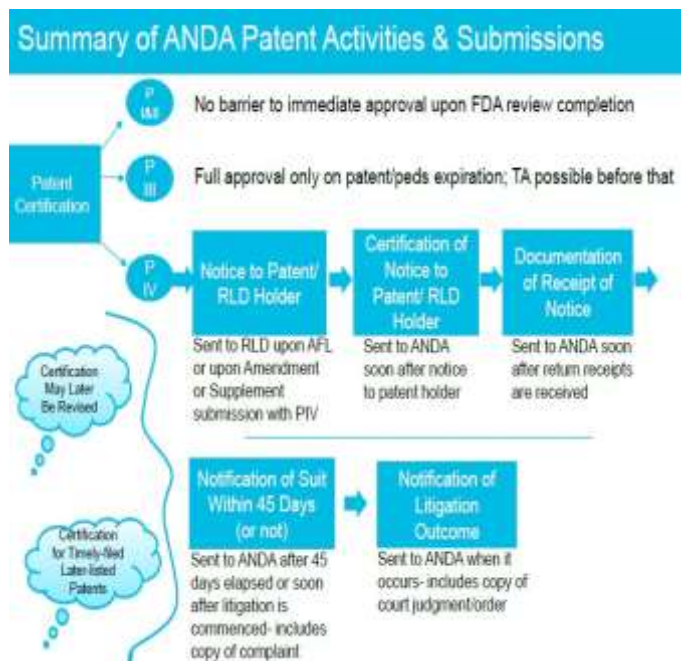
(11)

Requirements for successful Para –IV

Strong technical expertise to understand the technical intricacies of the patents

Expertise in IPR to decide how to challenge the patents

Strong financial background to meet the litigation cost (11)

**Figure 5. Overview of paragraphs I to IV(11)****REFERENCES**

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